

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934 or Section 30(h) of the Investment Company Act of 1940

| OMB APPROVAL | |
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|---|---|---|
| 1. Name and Address of Reporting Person * <u>CROOKE STANLEY T</u> (Last) (First) (Middle) <u>C/O ISIS PHARMACEUTICALS, INC.</u> <u>1896 RUTHERFORD ROAD</u> (Street) <u>CARLSBAD CA 92008</u> (City) (State) (Zip) | 2. Issuer Name and Ticker or Trading Symbol <u>ISIS PHARMACEUTICALS INC [ISIS]</u> | 5. Relationship of Reporting Person(s) to Issuer (Check all applicable) <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) <u>Chairman, President, CEO</u> |
| | 3. Date of Earliest Transaction (Month/Day/Year) <u>12/04/2009</u> | |
| | | 6. Individual or Joint/Group Filing (Check Applicable Line) <input checked="" type="checkbox"/> Form filed by One Reporting Person <input type="checkbox"/> Form filed by More than One Reporting Person |

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

| 1. Title of Security (Instr. 3) | 2. Transaction Date (Month/Day/Year) | 2A. Deemed Execution Date, if any (Month/Day/Year) | 3. Transaction Code (Instr. 8) | | 4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5) | | | 5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4) | 6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4) | 7. Nature of Indirect Beneficial Ownership (Instr. 4) |
|---------------------------------|--------------------------------------|--|--------------------------------|---|---|------------|----------|---|--|---|
| | | | Code | V | Amount | (A) or (D) | Price | | | |
| Common Stock | 12/04/2009 | 12/04/2009 | M ⁽¹⁾ | | 30,000 ⁽¹⁾ | A | \$6.8125 | 30,000 | D | |
| Common Stock | 12/04/2009 | 12/04/2009 | S ⁽²⁾ | | 30,000 ⁽²⁾ | D | \$10.55 | 0 | D | |
| Common Stock | 12/07/2009 | 12/07/2009 | M ⁽¹⁾ | | 30,000 ⁽¹⁾ | A | \$6.8125 | 30,000 | D | |
| Common Stock | 12/07/2009 | 12/07/2009 | S ⁽²⁾ | | 30,000 ⁽²⁾ | D | \$10.52 | 0 | D | |
| Common Stock | | | | | | | | 875,391 | I | By Trust |

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

| 1. Title of Derivative Security (Instr. 3) | 2. Conversion or Exercise Price of Derivative Security | 3. Transaction Date (Month/Day/Year) | 3A. Deemed Execution Date, if any (Month/Day/Year) | 4. Transaction Code (Instr. 8) | | 5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5) | | 6. Date Exercisable and Expiration Date (Month/Day/Year) | | 7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4) | 8. Price of Derivative Security (Instr. 5) | 9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4) | 10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4) | 11. Nature of Indirect Beneficial Ownership (Instr. 4) | |
|--|--|--------------------------------------|--|--------------------------------|---|--|--------|--|-----------------|---|--|--|---|--|-------|
| | | | | Code | V | (A) | (D) | Date Exercisable | Expiration Date | | | | | | Title |
| Employee Stock Option (right to buy) | \$6.8125 | 12/04/2009 | 12/04/2009 | M | | | 30,000 | 01/02/2002 | 01/05/2010 | Common Stock | 30,000 | \$0 | 220,000 | D | |
| Employee Stock Option (right to buy) | \$6.8125 | 12/07/2009 | 12/07/2009 | M | | | 30,000 | 01/02/2002 | 01/05/2010 | Common Stock | 30,000 | \$0 | 190,000 | D | |

Explanation of Responses:

- Acquired as a result of exercising a stock option that was scheduled to expire on 1/5/10. The purchase reported on this Form 4 was effected pursuant to a Rule 10b5-1 trading plan adopted by the reporting person on 2/15/08.
- The sale reported in this Form 4 was effected pursuant to a Rule 10b5-1 trading plan adopted by the reporting person on 2/15/08.

Remarks:

/s/Stanley T. Crooke

12/08/2009

** Signature of Reporting Person

Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.